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The Reaction of 2-Substituted Cycloalkanones with Aldehydes under Acidic Conditions

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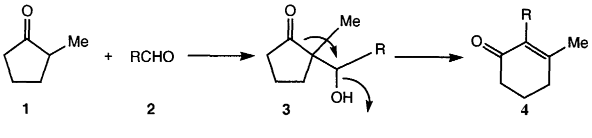
The title reaction proceeded with either ring enlargement or bicyclic compound formation, as well as the aldol reaction, depending upon the types of the reactants and reaction conditions.

The aldol reaction between ketones and aldehydes generally affords a mixture of many products, due to the involvement of self-condensation, reverse reaction, dehydration followed by Michael addition, among others. Therefore, the cross aldol reaction is usually carried out using some derivatives equivalent to the substrates, such as enol ethers for ketones, and acetals for aldehydes.[1)]

During our studies on the chemistry of β-stannyl ketones with Lewis acids, we noticed that 2-methylcyclopentanone reacted with benzaldehyde cleanly to undergo a ring enlargement under a Lewis acid treatment. Inspired by the results, we investigated the reactions of 2-substituted cycloalkanones with aldehydes under various conditions without any prior derivatization. It was found that the reaction proceeded fairly cleanly, affording several types of products depending upon the kinds of Lewis acids and aldehydes.

Results

When 2-methylcyclopentanone (**1**) was reacted with benzaldehyde **2a** or unsaturated aldehydes **2b**—**2e** under Lewis acid treatment, cyclohexenones **4a**—**4e** were obtained as major products (Eq. 1). The ring enlargement was also effected from **5** by the reaction with **2a** and **2b** (Eq. 2). The results are summarized in Table 1 (Runs a—j).



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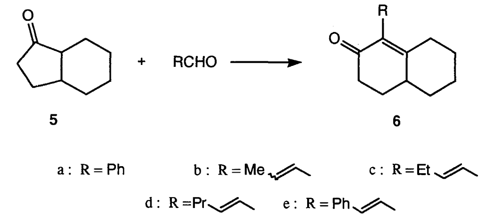


(2)

The reaction could be schemed as initiated by the aldol reaction producing **3**, followed by the elimination of the hydroxyl group and acyl migration. Expectedly the aldol **3a**, prepared according to the reported method,[2)] gave **4a** when treated with trimethylsilyl trifluoromethanesulfonate (TMSOTf) treatment (Run k).

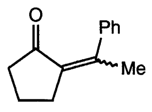
Although the acyl migration was exclusive in Runs a, f,

Table 1. Lewis Acid-Induced Reaction of Cycloalkanones or Aldols with Aldehydes

Run	Starting material	Aldehyde	Lewis acid	Product (yield %)[a)]					
a	**1**	**2a**	$AlCl_3$	**4a**	(62)				
b	**1**	**2a**	TMSOTf	**4a**	(67)	**7**	(ca. 15)		
c	**1**	**2a**	*n*-Bu_2BOTf	**4a**	(48)	**7**	(10)	**16f**	(8)
d	**1**	**2a**	$BF_3 \cdot OEt_2$	**4a**	(29)	**16f**	(ca. 20)		
e	**1**	**2b**	TMSOTf	**4b**-*trans*	(79)	**4b**-*cis*	(9)		
f	**1**	**2c**	TMSOTf	**4c**	(62)				
g	**1**	**2d**	TMSOTf	**4d**	(70)				
h	**1**	**2e**	TMSOTf	**4e**	(51)	**8**	(10)		
i	**5**	**2a**	TMSOTf	**6a**	(50)				
j	**5**	**2b**	TMSOTf	**6b**	(70)				
k	**3a**	—	TMSOTf	**4a**	(26)	**7**	(tr)		
l	**1**	**2a**	$TiCl_4$	**3a**	(12)				
m	**12f**	**13**	TMSOTf	**15f**	(26, 40[b)])				
n	**12f**	**13**	$AlCl_3$	**14f**	(75)				
o	**12g**	**2a**	TMSOTf	**16g**	(65)				
p	**12g**	**13**	TMSOTf	**15g**	(41, 52[b)])				
q	**12g**	**13**	$AlCl_3$	**14g**	(74)				
r	**14f**	—	TMSOTf	**15f**	(16)				
s	**14f**	**13**	TMSOTf	**15f**	(30)				
t	**14g**	—	TMSOTf	**15g**	(49)				

a) Yields are on the cycloalkanone basis. b) Using two equivalents of **13**.

g, i, and j, the methyl migration also occurred in Runs b and c, producing **7** as a minor product. An aldol condensation at the 5-position was also observed as a side reaction in Runs c and d, producing **16f** (Eq. 4). A small amount of by-product was isolated in Run h, to which the structure **8** was assigned in view of the spectroscopic data.[3] Presumably **8** was formed through an intramolecular S_N2' type reaction on the side chain of **3e** with C5 of the cyclopentanone ring. No products involving methyl migration, nor methylene migration were identified in the reactions with the unsaturated aldehydes. The minor product in Run e was assigned as a cis isomer, since it showed exactly the same mass spectrum as that of the major product, while it lacked the IR peak for the trans double bond at 969 cm^{-1} found in the major product.



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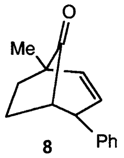

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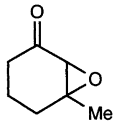

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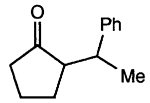

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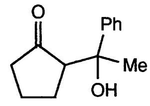
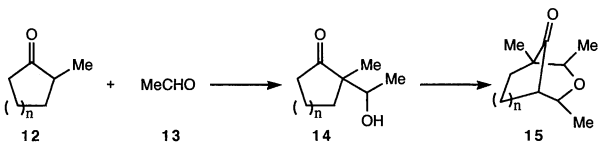


11

The structure of **4a** was confirmed by comparing with the authentic sample, prepared from **9** according to the reported method.[4] The structure of **7** (*trans–cis* mixture) was confirmed by the catalytic hydrogenation to afford **10** (diastereomer mixture), which indicated the IR absorption at 1736 cm^{-1}, suggesting the presence of five-membered ketone system. The attempted dehydration of **11**, obtained in small amount from the corresponding silyl enol ether and acetophenone,[5] resulted only in retro-aldol reaction to give acetophenone, without affording any amount of **7**.

The reaction terminated at the stage of aldol formation **3a**, when a mixture of **1** and **2a** was treated with $TiCl_4$ (Run l). However, no reaction proceeded with AgOTf, Et_3B, $SnCl_4$, or $FeCl_3 \cdot 6H_2O$. Characteristically $AlCl_3$ and BF_3–etherate did not induce the reaction of the unsaturated aldehydes **2b** and **2d** with **1**, contrary to the cases of benzaldehyde (Runs a and d).

In contrast to the ring enlargement with the aromatic or unsaturated aldehydes described above, the reaction type changed entirely when acetaldehyde **13** was used. The TMSOTf-induced reaction of **12f** (=**1**) with **13** afforded a bicyclic compound **15f** (Eq. 3), even with the use of only one equivalent of the aldehyde. The involvement of two molecules of the aldehyde was evident in view of the mass spectroscopic data. Presumably the reaction proceeded through a double aldol reaction at 2 and 5-positions of **12f**, followed by cyclization. Expectedly, the yield was improved by using two equivalents of **13** (Run m). The same type of the reaction occurred with **12g** upon treatment with TMSOTf, affording **15g** (Run p). Notably, **15f** was a single diastereomer as revealed from ^{1}H NMR (400 MHz) and ^{13}C NMR spectra, while **15g** was evidently a mixture of diastereomers in view of ^{1}H NMR analysis. Presumably, the whole reaction is controlled thermodynamically to afford the products as the most stable form. The bicyclic compounds **15f** and **15g** were also obtained from the respective mono-aldols **14f** and **14g** upon treatment with TMSOTf, irrespective of whether acetaldehyde was added or not (Runs r—t). Apparently the reactions in Runs r and t involved the retro-aldol reaction. The aldols **14f** and **14g** (diastereomer mixture) were prepared from the corresponding silyl enol ethers with **13** under the $TiCl_4$ treatment.[2]



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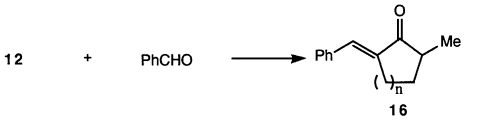


(4)

f: n=1 g: n=2

Unlike the cases of the five-membered ketone described above, no ring enlargement was observed in case of the six-membered ring system even with benzaldehyde. When **12g** was treated with **2a** in the presence of TMSOTf, the product was an α,β-enone **16g**, identical with the authenic sample prepared by the reported method.[7] (Eq. 4, Run o).

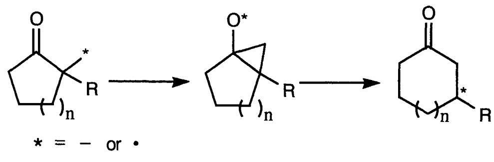
The reaction terminated at the stage of mono-aldols **14f** and **14g**, when the reactions of **12f** and **12g**, respectively, were induced with $AlCl_3$ (Runs n and q). The diastereoselectivity in these cases was a little higher than that obtained in the $TiCl_4$-induced aldol reaction of the corresponding silyl enol ethers.[2]

Discussion

It appears that all the reactions described in the present paper proceed through the initial aldol reaction at the more substituted α-position (2-position) of the cycloalkanones. It has been known that the reactions of 2-methylcyclohexanone and 2-methylcyclopentanone with some aldehydes in protic solvents proceed at the unsubstituted position (5- or 6-position) of the cycloalkanones followed by dehydration under both acidic and basic conditions.[6,7] Generally the benzylidene derivatives (*exo*-enones) are obtained under basic conditions, while benzyl derivatives (*endo*-enones) are obtained under acidic conditions.[8] It has been well documented that the aldol reaction is reversible and accompanied by a facile dehydration in protic solvents. Thus the thermodynamically most stable compounds might be the product under these conditions. On the other hand, the kinetic aldols can be isolated without being dehydrated, by starting from the corresponding derivatives of the substrates in aprotic solvents under mild conditions. Under these conditions, the reaction site is controlled by the regiochemistry of the enolates. The regioselective aldol reaction at the substituted position of the 2-substituted cycloalkanones has been elaborated by starting from the more substituted silyl enol ethers.[1] The silyl enol ethers or other metal enolates derived therefrom react with aldehydes to produce regiospecific aldols. The aldol reaction of the persubstituted enolates prepared in this way has been extensively studied, particularly from view point of the stereochemistry.[9] The formation of the persubstituted enolates has also been achieved from 2-bromo-2-methylcyclohexanone by treating with Zn-Et_2AlCl.[10]

The regiochemistry of the aldol reaction of the unsymmetrical cycloalkanones in aprotic solvents has received less attention. It is known that the aldol reaction of 2-methylcycloalkanones with benzaldehyde proceeds at the less hindered site, when promoted by tetraalkoxysilane/fluoride anion in dimethylformamide or without solvent.[11] The diethylaluminum tetramethylpiperidide-induced aldol reaction of 2-methylcyclohexanone in tetrahydrofuran is also known to react at the 6-position,[12] indicating that the enolization proceeds to afford the less substituted enolate. Therefore it is remarkable that the present reaction proceeded at the more hindered position. Although the aldols **3** and **14** were actually isolated in Runs 1, n, and q, the aldols underwent further reaction to result in either ring enlargement or retro-aldol reaction in other cases. Conceivably the ring enlargement reaction proceeded through (1) elimination of the hydroxyl group from the aldol, (2) concomitant 1,2-acyl migration, and (3) deprotonation, as shown in Eq. 1. Probably the series of the steps proceed only when elimination of the hydroxyl group (step 1) is facilitated through the cation-stabilizing effect by phenyl or alkenyl group, and the ring enlargement (step 2) does not give rise to the unfavorable strain, as would possibly be encountered in the *trans*-formation from six- to seven-membered ring system. Unless these requirements are fulfilled, the retro-aldol reaction proceeds to produce either **15** or **16**, depending upon whether the aldehyde is acetaldehyde or benzaldehyde, respectively. The γ-pyrone formation from 2,6-dialkylcyclohexanones under acidic conditions has been reported.[13]

The 1,2-acyl migration will be discussed next. A reaction scheme involving cyclopropoxyl radical or anion, resulted from the intramolecular addition of alkyl radical or anion to the carbonyl group is a well-documented process of 1,2-acyl migration (Eq. 5).[14] It seems likely, however, that the present ring enlargement involves a direct 1,2-acyl migration to the electron deficient carbon terminus rather than through the cyclopropoxy intermediates. This type of the acyl migration was first studied by House in the Lewis acid-induced reactions of α,β-epoxy ketones, and has been a target of many researchers (Eq. 6).[15] The unusually high migratory aptitude of the acyl group, as compared with that of methylene or hydride, has been established.[16] The 1,2-acyl migration proceeds concertedly with inversion of configuration at the migration terminus. Another instance of the Lewis acid-induced 1,2-acyl migration has been observed with pinacol–aldol system (Eq. 7).[17] Since the epoxy ketone could be looked as an equivalent to the aldol in a sense that the β-position of the carbonyl group has an oxygen leaving group, these examples could be assigned as precedence for the 1,2-acyl migration in the aldol system. However, it is highly likely that the acyl migration in these systems is effectively drived by the opening of oxirane or cyclobutanone ring, and also by the presence of a carbocation-stabilizing oxygen substituent at the migration origin carbon. Thus the present reaction is notable in that the 1,2-acyl migration is induced only with the participation of the alkenyl and aryl groups in stabilizing the cationic intermediates.



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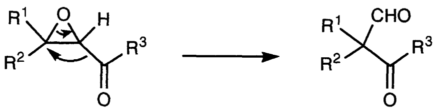

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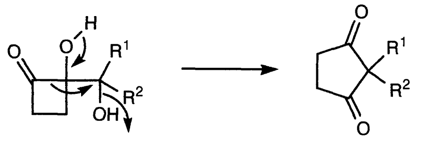

(7)

The base-induced reaction of the tosylate of **14g** has been reported to afford a mixture of cyclobutanone derivatives as well as a ring-opened product. However, neither acyl migration nor retro-aldol reaction has been observed.[18]

Remarkably the products from the unsaturated aldehydes have a unique system of 2-acyl-1,3-diene unit. To our best knowledge, only two cases have been reported for the preparation of this cross-conjugated electron-deficient diene system: the vinylation at α-position of α,β-epoxy ketones,[4] and the Robinson annulation of cycloalkanones with divinyl ketone.[19]

The phenylation at the α-position of α,β-epoxy ketones affording **6a** has been demonstrated as an example of α-alkylation and α-arylation of α,β-enones.[20,21]

Experimental

General Procedure and Instrumentation. GLC experiments were carried out on a 2.5 m×3 mm stainless steel column packed with Silicone SE 30 or Carbowax 20 M on silanized Chromosorb W. Column chromatography was carried out on Kieselgel 60, Art. 7734 (70—230 mesh ASTM). All the spectroscopic data were determined on a pure sample obtained by column chromatography. ^{1}H NMR spectra (60 MHz) were recorded on a Hitachi R-24 or JEOL PMX60 SI spectrometer. ^{1}H NMR (90 MHz) and ^{13}C NMR (22.5 MHz) spectra were measured on a Hitachi JNM-PMX 60 S R-90 H spectrometer, and 400 MHz ^{1}H NMR spectra on a JEOL GSX-400 spectrometer. GC-MS spectra were taken on a Shimadzu QP-1000 mass spectrometer, and high-resolution mass spectra on a JEOL DX-300 mass spectrometer. IR spectra were recorded on a Shimadzu IR-400 spectrometer. Unless otherwise stated, CH_2Cl_2 was used as a solvent for the column chromatography, CCl_4 solutions for ^{1}H NMR (60 MHz), $CDCl_3$ solutions for ^{1}H NMR (400 MHz) and ^{13}C NMR, and liquid film for IR measurement.

Reaction of 1 with 2a in the Presence of $AlCl_3$ (Run a). To a suspension of $AlCl_3$ (0.333 g, 2.5 mmol) in CH_2Cl_2 (10 ml) was added dropwise a CH_2Cl_2 solution (20 ml) of **1** (0.245 g, 2.5 mmol) and **2a** (0.265 g, 2.5 mmol) at room temperature during a period of 20 min. After stirred for additional 3 h at this temperature, aqueous $NaHCO_3$ was added and the products were extracted with CH_2Cl_2. The extract was dried over Na_2SO_4, and the solvent was removed in vacuo. The product was purified on a column chromatography to afford **4a** (0.287 g, 62%). IR 1665 and 1622 cm^{-1}. ^{1}H NMR δ=1.7—2.65 (m, 6H), 1.87 (s, 3H), and 6.8—7.45 (m, 5H). The compound **4a** was identical with the authentic sample prepared according to the reported method.[4]

Reaction of 1 with 2a in the Presence of TMSOTf (Run b). To a solution of **1** (0.245 g, 2.5 mmol) and **2a** (0.265 g, 2.5 mmol) in CH_2Cl_2 (20 ml) was added dropwise a CH_2Cl_2 solution (10 ml) of TMSOTf (0.555 g, 2.5 mmol) at room temperature during a period of 20 min. After stirred for additional 3 h, the reaction mixture was worked-up in the same way as described above. The column chromatography afforded **4a** (0.311 g, 67%) and **7** (0.102 g, 9%). In view of the ^{13}C NMR spectrum, **7** was a *trans-cis* mixture. For **7**, MS *m/z* 186 (M$^+$, base), 171, 153, 143, 128, 115, 91, 77, and 65. IR 1698, 1636, and 701 cm^{-1}. ^{1}H NMR δ=1.5—3.5 (m, 6H), 1.67 (d, *J*=2 Hz, 3H), and 7.11 (s, 5H). ^{13}C NMR[22] δ=[9.97*, 16.02], [31.17, 32.36*], [35.23, 36.77*], [39.68, 46.07*], 125.80, 127.93, 128.38, 139.09, 140.56, 156.56, and [210.24,* 210.74], (1:4). Found: *m/z* 186.1015. Calcd for $C_{13}H_{14}O$: M, 186.1044.

Upon catalytic hydrogenation (5% Pd–C/1 atm H_2/AcOEt, 35 h), **7** gave **10** in almost pure state as a diastereomer mixture (77% yield), as evident from ^{13}C NMR analysis. For **10**, MS *m/z* 188 (M$^+$), 173, 145, 117, 110, 97, 91 (base), and 65. IR 1736, 1453, and 699 cm^{-1}. ^{1}H NMR δ=0.96 and 1.20 (two doublets, *J*=8 Hz, 3H), 1.3—3.3 (m, 8H), and 7.10 (s, 5H). ^{13}C NMR[22] δ=[14.45*, 14.91], [25.67, 27.15*], [28.75, 29.74*], 36.01, [42.84, 44.35*], [49.62. 50.60], 125.94, 128.16, 128.75, and 139.68, (1:2). Found: *m/z* 188.1171. Calcd for $C_{13}H_{16}O$: M, 188.1201.

Reaction of 1 with 2a in the Presence of $(n\text{-Bu})_2BOTf$, $BF_3\cdot OEt_2$ (Runs c, d). The reactions were carried out in the same way as described for the TMSOTf-induced reaction (Run b). The respective produts and yields are shown in the Table 1. For **16f**,[11] ^{1}H NMR δ=1.13 (d, *J*=6 Hz, 3H), 1.3—3.5 (m, 6H), and 6.8—7.7 (m, 6H).

Reaction of 3a in the Presence of TMSOTf (Run k). The aldol **3a** was prepared according to the reported method.[2] ^{1}H NMR (diastereomer mixture) δ=0.67 (s, 1/4H), 0.98 (s, 3/4H), 1.15—2.20 (m 6H), 4.10 (br. s, 1H), 4.62 (s, 1H) 7.16 (s, 5H).

To a CH_2Cl_2 solution (45 ml) of **3a** (1.169 g, 5.73 mmol) was added dropwise a CH_2Cl_2 solution (23 ml) of TMSOTf (1.273 g, 5.73 mmol) in the ssme way as described for Run b. The products were **4a** (0.278 g, 26%) and **7** (trace).

Reaction of 1 with 2a in the Presence of $TiCl_4$ (Run l). The reaction was carried out in the same way as in Run b, from **1** (0.245 g, 2.5 mmol) and **2a** (0.265 g, 2.5 mmol) with $TiCl_4$ (0.480 g, 2.5 mmol). The product was indentical with the authentic **3a** prepared above, with the diastereomer showing at δ=0.67 as the major product.

Reaction of 1 with 2b, 2c, 2d, or 2e in the Presence of TMSOTf (Runs e, f, g, h). To a solution of **1** (0.245 g, 2.5 mmol) in CH_2Cl_2 (5 ml) was added dropwise a CH_2Cl_2 solution (5 ml) of TMSOTf (0.555 g, 2.5 mmol) at room temperature during a period of 15 min. After 15 min, a solution of **2b** (*trans*+*cis*), **2c** (*trans*), **2d** (*trans*), or **2e** (*trans*) (3 mmol) in CH_2Cl_2 (30 ml) was added during a period of 3.5 h. After stirred for additional 45 min at this temperature, the reaction mixture was worked-up in the same way as in Run a. While the products **4c**, **4d**, and **4e** were obtained as single isomers, **4b** was a mixture of *trans* and *cis* isomers, which were separated into each fraction on the column chromatography in yields as specified in the Table 1.

For *trans*-**4b**, MS *m/z* 150 (M$^+$), 135, 117, 107, 91, 79 (base), and 77. IR 1666, 1613, 1375, and 969 cm^{-1}. ^{1}H NMR δ=1.76 (d, *J*=6 Hz, 3H), 1.97 (s, 3H), 2.15—2.55 (m, 6H), and 5.9—6.1 (m, 2H). Found: *m/z* 150.1059. Calcd for $C_{10}H_{14}O$: M, 150.1045.

For *cis*-**4b**, MS same as that for the trans isomer. IR 1666, 1616, 1375, and 787 cm^{-1}. ^{1}H NMR δ=1.45 (d, *J*=6 Hz, 3H), 1.80 (s, 3H), 1.95—2.5 (m, 4H), and 5.4—6.0 (m, 2H). Found: *m/z* 150.1073. Calcd for $C_{10}H_{14}O$: M, 150.1045.

For **4c**, MS *m/z* 164 (M$^+$), 149, 135 (base), 131, 121, 107, 93, 91, 79, and 77. IR 1670, 1375, and 970 cm^{-1}. ^{1}H NMR δ=1.03 (t, *J*=6 Hz, 3H), 1.7—2.6 (m, 6H), 1.97 (s, 3H), and 5.8—6.1 (m, 2H). Found: *m/z* 164.1182. Calcd for $C_{11}H_{16}O$: M, 164.1201.

For **4d**, MS *m/z* 178 (M$^+$), 163, 149, 135 (base), 121, 107, 91, and 80. IR 1670, 1611, and 970 cm^{-1}. ^{1}H NMR δ=0.92 (dist. t, *J*=6 Hz, 3H), 1.1—2.7 (m, 10H), 1.97 (s, 3H), and 5.7—6.1 (m, 2H). Found: *m/z* 178.1361. Calcd for $C_{12}H_{18}O$: M, 178.1357.

For **4e**, MS *m/z* 212 (M$^+$), 197 (base), 179, 169, 155, 141, 115, 91, 77, and 65. IR 1668, 1626, 1375, and 970 cm^{-1}. ^{1}H NMR δ=1.97 (s, 3H), 1.5—2.5 (m, 6H), 6.77 and 6.93 (ABq, *J*=17 Hz, 2H), and 7.0—7.5 (m, 5H). Found: *m/z* 212.1175. Calcd for $C_{15}H_{16}O$: M, 212.1201.

For **8**,[3] MS *m/z* 212 (M$^+$, base), 197, 183, 155, 141, 128, 115, 91, and 77. IR 1732, 1236, and 1053 cm^{-1}. ^{1}H NMR δ=1.33 (s, 3H), 1.4—2.5 (m, 5H), 2.48 (d, *J*=6 Hz, 1H), 6.11 and 6.33

(ABq, J=15 Hz, 2H; upper halves further split to doublets with J=6 Hz), and 6.9—7.6 (m, 5H). ^{13}C NMR δ=16.54, 26.40, 29.22, 31.61, 45.28, 83.68, 123.58, 125.97, 127.24, 128.31, 134.06, 136.78, and 170.63. Found: m/z 1212.1216. Calcd for $C_{15}H_{16}O$: M, 212.1201.

Reaction of 5 with 2a in the Presence of TMSOTf (Run i). To a solution of **5**[23] (0.298 g, 2.16 mmol) and **2a** (0.229 g, 2.16 mmol) in CH_2Cl_2 (20 ml) was added dropwise a CH_2Cl_2 solution (10 ml) of TMSOTf (0.480 g, 2.16 mmol) at room temperature during a period of 20 min. After stirred for additional 3 h, the reaction mixture was worked-up and purified as in Run a, to afford **6a**[20] (0.243 g, 50%). MS m/z 226 (M^+, base), 198, 169, 153, 141, 129, 104, 91, and 77. IR 1671 cm^{-1}. ^{1}H NMR δ=0.60—2.83 (m, 13H) and 6.63—7.53 (m, 5H). ^{13}C NMR[24] δ=24.99†, 26.78†, 28.01†, 32.11†, 34.59†, 36.06†, 38.18, 126.10, 127.07, 129.28, 134.88†, 135.45†, 160.73†, and 196.72†. Found: m/z 226.1366. Calcd for $C_{16}H_{18}O$: M, 226.1358.

Reaction of 5 with 2b in the Presence of TMSOTf (Run j). To a solution of **5** (0.204 g, 1.48 mmol) in CH_2Cl_2 (5 ml) was added dropwise a CH_2Cl_2 solution (5 ml) of TMSOTf (0.329 g, 1.48 mmol) at room temperature during a period of 15 min. After 15 min, a solution of **2b** (0.124 g, 1.78 mmol) in CH_2Cl_2 (30 ml) was added during a period of 3.5 h. After stirred for additional 45 min at this temperature, the reaction mixture was worked-up and purified as above, to afford **6b** (0.197 g, 70%). MS m/z 190 (M^+, base), 175, 161, 147, 119, 105, 91, and 79. IR 1670, 1612, 1488, and 967 cm^{-1}. ^{1}H NMR δ=1.20—2.50 (m, 13H), 1.78 (d, J=5.2 Hz, 3H), and 5.40—6.17 (m, 2H). ^{13}C NMR[24] δ=18.09, 24.95†, 26.67†, 27.64†, 31.19†, 34.50†, 35.99†, 38.49, 123.27, 129.94, 130.53†, 159.16†, and 197.48†. Found: m/z 190.1352. Calcd for $C_{13}H_{18}O$: M, 190.1358.

Reaction of 12f with 13 in the Presence of TMSOTf (Run m). To a solution of **12f** (0.245 g, 2.5 mmol) in CH_2Cl_2 (10 ml) was added dropwise a CH_2Cl_2 solution (10 ml) of TMSOTf (0.278 g, 1.25 mmol) at room temperature during a period of 10 min. After 15 min, a solution of **13** (0.110 g, 2.5 mmol) in CH_2Cl_2 (10 ml) was added during a period of 30 min, and stirred for additional 1.2 h at this temperature. The same work-up as above afforded **15f** (0.109 g, 26%). MS m/z 168 (M^+), 124, 96, 71, 69 (base), and 55. IR 1745, 1379, and 1082 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ=0.93 (s, 3H), 1.20 (d, J=6.2 Hz, 3H), 1.26 (d, J=6.2 Hz, 3H), 1.39—1.48 (m, 1H), 1.69—1.79 (m, 1H), 1.95—2.40 (m, 1H), 2.15—2.24 (m, 2H), 3.55 (q, J=6.2 Hz, 1H), and 3.93 (q, J=6.2 Hz, 1H). ^{13}C NMR δ=13.87, 15.27, 16.55, 18.66, 24.60, 51.00, 52.39, 78.88, 82.93, and 218.49. Found: m/z 168.1158. Calcd for $C_{10}H_{16}O_2$: M, 168.1150.

The yield was improved to 40%, when 5.0 mmol (2 equiv) of **13** was used.

In the same way, **12g** afforded **15g**, in yields shown in the Table 1 (Run p). MS m/z 182 (M^+), 138, 123, 110, 95, 82 (base), 81, 69, 68, and 67. IR 1718, 1380, and 1124 cm^{-1}. ^{1}H NMR δ=0.83 (s, 3H), 1.21 (d, J=6 Hz, 3H), 1.23 (d, J=6 Hz, 3H), 1.4—2.9 (m, 7H), 3.44 (q, J=6 Hz, 1H), and 3.82 (q, J=6 Hz, 1H). Found: m/z 182.1321. Calcd for $C_{11}H_{18}O_2$: M, 182.1307.

Reaction of 12f with 13 in the Presence of $AlCl_3$ (Run n). To a suspension of $AlCl_3$ (0.333 g, 2.5 mmol) in CH_2Cl_2 (10 ml) was added dropwise a CH_2Cl_2 solution (10 ml) of **12f** (0.246 g, 2.5 mmol) at room temperature during a period of 10 min. After 15 min, a CH_2Cl_2 solution (10 ml) of **13** (0.110 g, 2.5 mmol) was added during a period of 20 min. After stirred for additional 3.5 h at this temperature, the reaction mixture was worked-up in the same way as above to afford **14f** (0.298 g, 75%). The product was identical with that prepared according to the reported method,[2] which was separated into two diastereomers on a column chromatography (silica gel, hexane–ether=3/1). For diastereomer-I, IR 3446, 1731, and 1059 cm^{-1}. ^{1}H NMR δ=1.00 (s, 3H), 1.06 (d, J=6 Hz, 3H), 1.2—2.5 (m, 6H), 3.68 (q, J=6 Hz, 1H), and 3.67 (s, 1H). For diastereomer-II, ^{1}H NMR δ=0.83 (s, 3H), 1.09 (d, J=6 Hz, 3H), 1.2—2.5 (m, 6H), 3.55 (br. s, 1H), and 3.82 (q, J=6 Hz, 1H).

In the same way, **12g** (0.140 g, 1.25 mmol) gave **14g** (0.746 g, 74%)[18] as a diastereomer mixture (Run q), which was identical with that prepared according to the reported method.[2] ^{1}H NMR δ=0.9—1.15 (a couple of singlets and doublets, 6H), 1.5—2.7 (m, 8H), 3.47 (bs. s, 1H), and 3.9—4.3 (m, 1H).

Reaction of 12g with 2a in the Presence of TMSOTf (Run o). Using **12g** (0.280 g, 2.5 mmol), the reaction was carried out in the same way as in Run b, to afford **16g** (0.324 g, 65%). The product was identical with that prepared by the reported method.[7] ^{1}H NMR, δ=1.12 (d, J=7 Hz, 3H), 1.3—3.2 (m, 7H), 7.25 (s, 6H).

Reaction of 14f in the Presence of TMSOTf (Run r). To a CH_2Cl_2 solution (20 ml) of **14f** (0.336 g, 2.36 mmol) was added dropwise a CH_2Cl_2 solution (10 ml) of TMSOTf (0.524 g, 2.36 mmol) at room temperature during a period of 30 min. The mixture was worked-up in the same way as above to give **15f** (0.061 g, 16%). The yield was improved when the reaction was carried out in the otherwise same way with **13** added (Run s).

In the same way, **14g** (0.390 g, 2.5 mmol) gave **15g** (0.224 g, 49%) (Run t).

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